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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,207	OSHIMURA ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,21,23,26-28,33,37-46,49 and 52* is/are pending in the application.

4a) Of the above claim(s) *1-17 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20,21,26-28,33,37-46,49 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 15, 2010 has been entered.

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on June 27, 2008 is acknowledged. Applicant has elected the invention of Group III, claim(s) 18-23, 26-28, 33 and 37-48, drawn to a method of making a human artificial chromosome vector comprising obtaining cells that retain human chromosome 21 and deleting a distal region of the long or short arm of the human chromosome 21.

Within Group III, Applicant has elected the deletion site species "AL163204", which is located in the long arm of human chromosome 21.

Amendments

In the reply filed February 15, 2010, Applicant has cancelled Claims 19, 22, 24-25, 29-32, 34-36 and 47-48 and 50-51, withdrawn Claims 1-17 and 23, amended Claims 18, 37, 41, 42 and 46, and added new claims, Claim 52.

Claims 1-17 and 23 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 18, 20-21, 26-28, 33, 37-46, 49 and 52 are under consideration.

Priority

This application is a 371 of PCT/JP03/12734, filed on October 3, 2003. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies, but not English translations, of PCT/JP03/12734, filed on October 3, 2003 and JP2002-202853 filed on October 4, 2002 have been filed with the instant application.

Accordingly, the effective priority date of the instant application is granted as October 4, 2002.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 15, 2010 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

1. **The prior rejection of Claims 41 and 46 under 35 U.S.C. 112, first paragraph, is withdrawn** in light of Applicant's amendment to the claims limiting the scope to mouse embryonic stem cells.

2. **Claims 18, 21, 26-28, 33 and 52 are rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the relationship between the cell (step (a)) in which the HAC is produced and the structural element that confers the functional property of mitotic stability. The claims recite that the vector is mitotically stable when transferred from DT40 cells to CHO cells or human cells, thereby indicating a structural property is conferred onto the HAC by the DT40 cells. However, the method of producing the HAC does not require the use of DT40 cells whatsoever, nor that the HAC must be transferred from a first cell to DT40 cells before being subsequently transferred to a third cell type. Thus, the 'wherein' clause is merely descriptive for a specific condition not required by the claimed method steps. Furthermore, the 'wherein' clause indicates that the HAC is mitotically unstable unless it is first transferred into DT40 cells. However, the specification fails to disclose that the DT40 cells confer a structural property onto the HAC not conferred by any other cell type so that the product HAC will become mitotically stable. Thus, it the relationship between the DT40 cells and the structural and functional property(ies) of the product HAC is unclear.

Appropriate correction is required.

3. **Claims 18, 20, 26-28, 33, 37-46, 49 and 52 are rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the introduction of a telomere sequence onto the remaining portion of the 21q11 region of the long arm of the human chromosome 21. Those of ordinary skill in the art recognize that the absence of telomere sequences renders the nucleic acid molecule unstable, and thus the claimed method steps will fail to achieve a mitotically stable artificial chromosome, absent evidence to the contrary. The claims as written fail to require the necessary telomere sequence on the remaining portion of the 21q11 region of the long arm of the human chromosome 21. The specification discloses that while a distal portion the 21q11 region of the long arm of the human chromosome 21 is deleted, the remaining portion of 21q11 retains a telomere sequence, e.g. telomere truncation or substitution with a telomere sequence (pgs 21-22, joining ¶). The working example (Example 1) discloses the deletion step is a telomere truncation method step as per Kuroiwa et al (1998; of record) which retains telomere sequences. Furthermore, it is unclear how passaging the mitotically unstable HAC lacking a telomere sequence on the remaining portion of 21q11 through DT40 cells will render said unstable HAC mitotically stable when transferred to CHO or human cells.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. **The prior rejection of Claims 18, 20-21, 26-27, 33 and 37-46 under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (1998; *of record in IDS**)** in view of Kuroiwa et al (2000; *of record in IDS), Tomizuka et al (1997; *of record in specification) and Saffery et al (J. Gene Med. 4:5-13, 2002; *of record in IDS) **is withdrawn** in light of Applicant's amendment to the claims, specifically "at AL163204", a limitation that neither Kuroiwa (1998, 2000), Tomizuka nor Saffery teach.

5. **Claims 28 and 49 stand, and Claims 18, 20-21, 26-27, 33, 37-46 and 52 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (1998; *of record in IDS) in view of Kuroiwa et al (2000; *of record in IDS) and Tomizuka et al (1997; *of record in specification), Saffery et al (2002; *of record in IDS) and Hattori et al (2000, *of record).

Response to Arguments

Applicant argues that deletion of the specific area [a distal region within the 21q11 region] and keeping the remaining positions are crucial for obtaining a HAC vector that can be transferred to human somatic cells and retained stably in such cells. There was no suggestion in the prior art that this outcome might be occasioned.

Applicant's argument(s) has been fully considered, but is not persuasive. Kuroiwa et al (1998) taught a method for producing a human artificial chromosome vector, the method comprising the step of telomere truncation, as was practiced in the instant application. Thus, at the time of the instantly asserted invention, those of ordinary skill in the art possessed a reasonable expectation of success that practicing telomere truncation on other human chromosomes would also occasion mitotically stable HAC vectors.

Applicant argues that at the time the invention was made, human chromosome 21-based HACs were not stable in cells. Instead, there were technical difficulties in obtaining the stably retained human chromosome 21-based HAC as disclosed in the present application. Accordingly, there was no metric or principle to guide "routine design" in this regard; nor was there basis for a reasonable (i.e., a principled) expectation of success in finding the deletion positions as proposed.

Applicant's argument(s) has been fully considered, but is not persuasive. It is unclear what element of routine molecular biology Applicant considers to deny the basis for a reasonable [principled] expectation of success to the ordinary artisan in a method of making a hChr 21 HAC vector. Kuroiwa (1998, 2000) and Tomizuka taught efficient methods to make mitotically stable HAC vectors. The claimed method steps are essentially identical to the teachings of Kuroiwa, save for the targeted location of hChr 21 21q11. Furthermore, Hattori taught the locations of reported, 21q11 transcribed loci distal to the hChr 21 centromere, specifically C21orf15 and CYP4F3LP that are encoded within [at] AL163204. Thus, it is considered common sense design choice for the ordinary artisan to perform telomere truncation at AL163024 on 21q11 so as to remove most, if not all, known transcribed genes from an HAC vector, thereby avoiding any potential detrimental effects due to the expression of the extraneous gene(s). Thus, a general

principle to guide "routine design", specifically the deletion of most, if not all, genes distal to the centromere, had been established in the prior art.

Applicant argues that Saffery describes the problems associated with the production of useful and stable HACs, i.e. [HACs] are large entities and are therefore difficult to fully characterize, the large size of HACs also makes them difficult to manipulate in terms of the introduction of genes and the transfer from cell to cell in an intact form [structurally and mitotically stable]. Because of the large size of these vectors, the skilled artisan also would not have known which region(s) of the HAC, if any, could be deleted to obtain a stable HAC.

Applicant's argument(s) has been fully considered, but is not persuasive. Kuroiwa (1998, 2000) and Tomizuka demonstrated that those of ordinary skill in the art prior to the instantly claimed invention possessed the routine means and ability to fully characterize HACs and transfer large HACs from a first cell type to a second cell type.

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). See MPEP §2164.06. In the instant case, Kuroiwa (1998, 2000) and Tomizuka demonstrate that making HACs and characterizing their structural and functional properties is routine experimentation.

Applicant argues that applicants show that deletion of this specific area of chromosome 21 creates a HAC vector that (1) can be stably transferred to human normal fibroblasts and to human normal somatic cells other than fibroblasts and that (2) is retained stably, for instance, in chicken cell lines and human cell clones and in human stem cells. These results are unexpected because, at the time the present invention was made, the prior art taught that human artificial

chromosomes were not stable in mammalian cells. The Saffery reference itself supports this understanding, given its observation that, "on transfer back into CHO or human cells, mitotic segregation was compromised with a high degree of variability in the copy number of the minichromosome and increased mitotic loss rates". Dependent claim 52 mandates that such mitotic stability persist for at least 22 divisions. Accordingly, there was a clear prejudice in the art against transferring an artificial chromosome into mammalian cells, which in turn underscores the surprising aspects of applicants' claimed invention.

Applicant's argument(s) has been fully considered, but is not persuasive.

As a first matter, Arguments of counsel cannot take the place of **factually supported objective evidence** in the record. See *In re Schulze*, 346 F.2d 500, 602, 145 USPQ 716, 718 (CCPA 1965), *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Attorney statements regarding, e.g. unexpected results, are not evidence without a supporting declaration.

As a second matter, Applicant's unexpected results are not commensurate in scope to the claims. Applicant's asserted unexpected results reflect HACs possessing telomere sequences at both ends of the chromosome. However, as discussed in the rejections above under 35 U.S.C. 112, second paragraph, above, only Claim 21 requires telomere sequences present at both ends of the chromosome.

As a third matter, the claimed method for producing a HAC does not require a production step within CHO or human cells. Completion of the product HAC is fully achieved per the artisan's steps of "obtaining", "deleting" and "inserting". Rather, the 'wherein' clause functional limitation [mitotic stability] merely describes a property under an arbitrary and optional condition [when transferred to CHO or human cells] after the HAC has been produced. However,

"Products of identical chemical composition can not have mutual exclusive properties." A compound and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical [HAC] structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP §2112.01. The burden is shifted to the applicant to show that the prior art product [HAC vector] does not inherently possess the same properties as the instantly claimed product.

As a fourth matter, Kuroiwa (2000) taught efficient methods to make mitotically stable HAC vectors, wherein said vectors were mitotically stable, for at least 70 divisions, when transferred from DT-40 cells to mammalian ES cells. Saffery et al taught the art recognized the ability of HAC vectors to be mitotically stable in human cells for over 180 days without selection (pg 6, col. 2), which is equivalent to at least 166 divisions.

Furthermore, to rebut Applicant's assertion that mitotic stability for at least 22 divisions is an unexpected result, the Examiner provides a copy of Masumoto et al (Chromosoma 107:406-416, 1998) and Rasheed et al (Cancer 33:1027-1033, 1974) as evidentiary references regarding the state of the art at the time of the invention.

Masumoto et al taught the ability of a HAC vector derived from human chromosome 21 (hChr 21; Figure 1) that is mitotically stable for at least 60 days when transferred to human HT1080 cells (Figure 3). Rasheed et al taught that human HT1080 cells have a cell doubling/division time of 26 hours (Table 1). Thus, Masumoto et al taught the ability of a HAC vector derived from human chromosome 21 (hChr 21) that is mitotically stable for at least 55 divisions when transferred to human cells.

Accordingly, the Examiner maintains the position that at the time of the instantly asserted invention, those of ordinary skill in the art possessed a reasonable expectation in success for producing a human artificial chromosome vector comprising deleting a distal region at AL163204 within the 21q11 region of the long arm of the human chromosome 21, wherein said vector is mitotically stable in CHO or human cells for at least 22 divisions.

Applicant argues that Hattori suggests nothing about deleting a distal region within the 21q11 region of the long arm. As such, Hattori fails to cure the deficiencies of Kuroiwa '98, Kuroiwa '00, Tomizuka, or Saffery alone or in combination

Applicant's argument(s) has been fully considered, but is not persuasive. Kuroiwa (1998) taught efficient methods to make mitotically stable HAC vectors comprising the step of deleting most, if not all, genes distal to the centromere. The instantly claimed method steps are essentially identical to the teachings of Kuroiwa, save for the targeted location of hChr 21, 21q11. Hattori taught the locations of reported, transcribed 21q11 loci distal to the centromere, specifically C21orf15 and CYP4F3LP that are encoded within [at] AL163204. Thus, it is considered common sense design choice for the ordinary artisan to perform telomere truncation at AL163024 on 21q11 so as to remove most, if not all, known transcribed genes from an HAC vector, thereby avoiding any potential detrimental effects due to the expression of the extraneous gene(s). Thus, a general principle to guide "routine design", specifically the deletion of most, if not all, genes distal to the centromere, had been established in the prior art.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633